

### REMARKS

Claims 1-14 are currently pending in the application. Claims 2, 8, and 14 are canceled. Claim 1 is amended. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

#### **35 U.S.C. §102(b) Rejection**

Claims 1-14 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Agrawal et al. (WO 94/01550). The Examiner states that Agrawal discloses antisense oligonucleotides that are “self stabilized,” and that it further discloses “antisense that have a first region and a second region that bind a target sequence wherein the first region is available for binding while the second region is temporarily ‘masked’.”

The Examiner points to the disclosure within Agrawal that states:

“disruption and replacement of base-pairing takes place because the intermolecular base-paired structure formed by the hybrid between the target nucleic acid sequence and the target hybridization is more thermodynamically stable than the intra-molecular base-paired structure formed by the self-complementary oligonucleotide.”

The Examiner further points to the definition of “stabilizing elements” within the instant specification, which the Examiner characterizes that “the aim of the elements is to render the second region/target hybrid more stable than the second region in its masked states.” The Examiner asserts from this that “since Agrawal et al have disclosed this characteristic in the self-stabilized oligonucleotide these oligonucleotides, without evidence to the contrary, inherently contain some destabilizing element.” Applicants respectfully disagree.

With this Amendment, Applicants have amended claim 1, such that the limitations within presently canceled claims 2 and 8 were incorporated. Claim 1, is currently amended to recite the additional limitation that “said second region is temporarily masked through being comprised in a hairpin loop structure, **wherein said hairpin loop structure comprising said second region contains one or more destabilising elements.**” (emphasis added). Support for destabilising elements can be found within the Specification. For example, in paragraph [0038] it is stated:

[0038] Destabilising elements may be incorporated in the antisense molecules according to the invention in order to favour unmasking thereof and hybridisation of the second region to the target sequence. In particular, where the second region is masked through incorporation into a stem/loop or hairpin structure, **base pair mismatches, G-U base pairings and incorporation of extra bases in one strand in order to cause bulging may be used to induce destabilisation.** The aim is to render the second region/target hybrid more stable than the second region in its masked state, thus thermodynamically favouring the formation of the hybrid. (emphasis added)

In addition, in paragraph [0050] it is stated:

[0050] The stem/loop of the hAS molecule preferably contains destabilising elements (**bulges, mismatches, G-U pairs**) to render its unwinding, and the association with the target nucleic acid molecule, energetically highly favourable. (emphasis added)

“To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is **necessarily present** in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.” (emphasis added) **In re Robertson**, 169 F.3d 743 (Fed. Cir. 1999) (citing **Continental Can Co. USA, Inc. v. Monsanto Co.**, 948 F.2d 1264 (Fed. Cir. 1991)). Applicants assert that the Agrawal reference does **not** inherently anticipate use of destabilising elements as disclosed herein, because the destabilising element is not an element that is necessarily present in the embodiment of Agrawal pointed to by the Examiner. For example, in Example 4 of Agrawal entitled “**Stability of Duplexes Between Self-Stabilized Oligonucleotides and Complementary Oligos**,” it is disclosed that “**intramolecular base pairing** involving the self-complementary region [of CMPD B] **is less thermodynamically stable than the intermolecular base pairing** between the target hybridizing region and a complementary oligonucleotide” (emphasis added). The structure of CMDP B is disclosed in Figure 5, and does **not** contain any destabilising element as described in the instant application. As such, the teachings of the Agrawal reference firmly establish that destabilising elements need not be present in order for the intermolecular base-paired structure formed by the hybrid between the target nucleic acid sequence and the target hybridization to be more thermodynamically stable than the intra-molecular base-paired structure formed by the self-complementary oligonucleotide. In view above and the amendments to claim 1 made herein, the molecules

taught by Agrawal do not inherently contain some destabilising element. Therefore, Applicants submit that claim 1, as amended, is novel over Agrawal and respectfully request that the §102(b) rejection over the pending claims be withdrawn.

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

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